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=> d his

     (FILE 'HOME' ENTERED AT 13:45:09 ON 15 APR 2004)

     FILE 'REGISTRY' ENTERED AT 13:45:32 ON 15 APR 2004
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L2           3 S L1 SSS FULL

     FILE 'CAPLUS' ENTERED AT 13:45:51 ON 15 APR 2004
L3          20 S L2
L4           3 S L3 AND CRYSTAL?

=>  d bib abs 1-3

L4   ANSWER 1 OF 3  CAPLUS  COPYRIGHT 2004 ACS on STN
AN   2001:851135  CAPLUS
DN   135:371993
TI   Methods for crystallization of N-(1(S)-ethoxycarbonyl-3-
     phenylpropyl)-L-alanine N-carboxyanhydride
IN   Fukae, Masafumi; Ueda, Yasuyoshi
PA   Kaneka Corporation, Japan
SO   PCT Int. Appl., 41 pp.
     CODEN: PIXXD2
DT   Patent
LA   Japanese
FAN.CNT 1
     PATENT NO.         KIND  DATE           APPLICATION NO.  DATE
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PI   WO 2001087858      A1    20011122       WO 2001-JP4059   20010515
         W:  AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,
             CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,
             GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,
             LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT,
             RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US,
             UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
         RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY,
             DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF,
             BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG
     AU 2001056758      A5    20011126       AU 2001-56758    20010515
     SI 20817           C     20020831       SI 2001-20002    20010515
     EP 1283204         A1    20030212       EP 2001-930174   20010515
         R:  AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
             IE, SI, LT, LV, FI, RO, MK, CY, AL, TR
     TW 527351          B     20030411       TW 2001-90111623 20010515
     HR 2002000122      A1    20030430       HR 2002-122      20020211
     US 2002137944      A1    20020926       US 2002-19318    20020424
PRAI JP 2000-141717     A     20000515
     JP 2000-330339     A     20001030
     JP 2000-352892     A     20001120
     WO 2001-JP4059     W     20010515
AB   A solution of N-(1(S)-ethoxycarbonyl-3-phenylpropyl)-L-alanine
     N-carboxyanhydride (I) in a good solvent therefor is added to an aliphatic
     hydrocarbon solvent to crystallize the N-carboxy anhydride while
     inhibiting the compound from separating out as an oily matter or scale.  In
this
     process, an aliphatic hydrocarbon solvent is gradually added to a solution of I
     in a good solvent therefor at a temperature of 60° or lower over a 1/4 h
     or longer to crystallize I.  This process is suitable for
     crystallization of I in an industrial scale without oil formation or scaling to
     give I of high purity with large grain diameter, good powder characteristic,
     and good handlability.  I is used as an common intermediate for a series
     of angiotensin converting enzyme inhibitors which are used for the
     treatment of hypertension.  Thus, 32 g COCl2 was blown into a solution of 25
     g N-[1(S)-ethoxycarbonylphenylpropyl]-L-alanine in 500 mL CH2Cl2, refluxed
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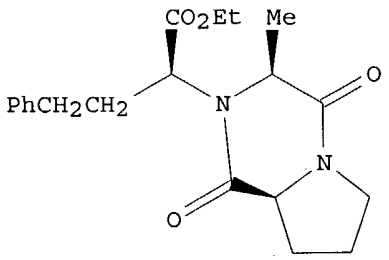
for 8 h on an oil bath (50°), distilled to remove $CH_2Cl_2$ containing $COCl_2$ and HCl, and treated with $CH_2Cl_2$ to give a .apprx.62 weight% solution of I in $CH_2Cl_2$ (98% yield). The above solution (63.2 g) was added dropwise to 250 mL n-cyclohexane at -12° over a period of 1 h, stirred at the same temperature for 1 h in a good solvent/aliphatic hydrocarbon solvent weight ratio of 0.15. The precipitated I **crystals** were filtered under reduced pressure, washed with 50 mL n-hexane, and dried at 25° for 1 h under reduced pressure to give I (93% recovery, 98% purity, ≤99% e.e. optical purity, and average grain diameter 50 μm). An amount of scaling adhered on the wall of the vessel was .apprx.6 weight%.

RE.CNT 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 2 OF 3 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1999:96261 CAPLUS
DN 130:168658
TI Process for preparing pharmacologically acceptable salts of N-[1(S)-ethoxycarbonyl-3-phenylpropyl]-L-alanyl amino acids
IN Ueda, Yasuyoshi; Kinoshita, Koichi; Moroshima, Tadashi; Yanagida, Yoshifumi; Fuse, Yoshihide
PA Kaneka Corporation, Japan
SO PCT Int. Appl., 97 pp.
CODEN: PIXXD2
DT Patent
LA Japanese
FAN.CNT 1

| | PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|---|
| PI | WO 9905164 | A1 | 19990204 | WO 1998-JP3240 | 19980721 |
| | W: CA, CN, HU, IL, JP, KR, SG, SI, US | | | | |
| | RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE | | | | |
| | IN 184759 | A | 20000923 | IN 1998-CA1259 | 19980720 |
| | EP 967221 | A1 | 19991229 | EP 1998-932585 | 19980721 |
| | R: AT, CH, DE, ES, FR, GB, IT, LI, NL, IE | | | | |
| | US 6335453 | B1 | 20020101 | US 1999-269107 | 19990319 |
| | IN 186699 | A | 20011027 | IN 1999-CA795 | 19990916 |
| | IN 187670 | A | 20020601 | IN 1999-CA796 | 19990916 |
| | US 2002087007 | A1 | 20020704 | US 2001-989186 | 20011121 |
| | US 6518436 | B2 | 20030211 | | |
| | US 2003105327 | A1 | 20030605 | US 2002-295897 | 20021118 |
| | US 6713628 | B2 | 20040330 | | |
| PRAI | JP 1997-195865 | A | 19970722 | | |
| | IN 1998-CA1259 | A | 19980720 | | |
| | WO 1998-JP3240 | W | 19980721 | | |
| | US 1999-269107 | A3 | 19990319 | | |
| | US 2001-989186 | A3 | 20011121 | | |

OS CASREACT 130:168658; MARPAT 130:168658
GI




II

AB Claimed is a process for preparing pharmacol. acceptable salts of N-[1(S)-ethoxycarbonyl-3-phenylpropyl]-L-alanyl amino acids, comprising the steps of: condensing an amino acid with N-[1(S)-ethoxycarbonyl-3-phenylpropyl]-L-alanine N-carboxy anhydride (I) under basic conditions; decarboxylating the condensate under neutral to acidic conditions to prepare an N-[1(S)-ethoxycarbonyl-3-phenylpropyl]-L-alanyl amino acid; and converting the product to a pharmacol. acceptable salt thereof, characterized in that a series of procedures up to the formation of a pharmacol. acceptable salt or up to the withdrawal of the pharmaceutically acceptable salt thereof are carried out in an aqueous liquid to inhibit the production of a byproduct diketopiperazine, e.g. II. According to this process, high-quality pharmacol. acceptable salts of N-[1(S)-ethoxycarbonyl-3-phenylpropyl]-L-alanyl amino acids can be prepared in high yields in a cost-effective manner on a com. scale. Thus, a solution of 29.20 g I in 156 mL EtOAc was slowly added dropwise over 4 h at 19-20° to a mixture of 22.02 g L-proline, 20 mL EtOAc, and 22 mL H2O (adjusted to pH 10.5 by adding 30 weight% aqueous NaOH) with stirring, while the pH of the reaction mixture was kept at pH 10.5±0.5 by adding 30 weight% aqueous NaOH during the reaction. After completing the addition, the reaction mixture was stirred for another 1 h under the same condition, warmed to 30°, made pH 4.5±0.2 by adding 35% weight% aqueous HCl, and stirred for 10 min to complete decarboxylation. The organic phase was separated and the aqueous phase was extracted once with EtOAc. The extract was combined and washed once with 5% volume of H2O to give the water-saturated organic phase containing N-[1(S)-ethoxycarbonyl-3-phenylpropyl]-L-alanyl-L-proline (enalapril) (III) 14, II 0.5, N-[1(S)-carboxy-3-phenylpropyl]-L-alanyl-L-proline 0.4, and N-[1(S)-ethoxycarbonyl-3-phenylpropyl]-L-alanine 0.5 weight%. To the organic phase was added 10.49 g maleic acid and the resulting mixture was stirred at 30° for 1 h, cooled to 3° over 3 h, and was stirred for another 2 h to give, after filtration of the precipitated **crystals**, washing them with EtOAc chilled to 5°, and vacuum drying, 90% III maleate of ≥99% purity.

RE.CNT 25 THERE ARE 25 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 3 OF 3 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1998:794984 CAPLUS
DN 130:38308
TI Process for obtaining quinapryl hydrochloride and solvates useful for isolating and purifying quinapryl hydrochloride
IN Monsalvatje Llagostera, Montserrat; Bartra Sanmarti, Marti; Tomas Navarro, Jaime; Puig Torres, Salvador
PA Esteve Quimica, S.A., Spain
SO PCT Int. Appl., 29 pp.
CODEN: PIXXD2
DT Patent
LA Spanish
FAN.CNT 1

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| PI WO 9854149 | A1 | 19981203 | WO 1998-ES145 | 19980525 |
| W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | | |
| RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG | | | | |
| ES 2122941 | A1 | 19981216 | ES 1997-1169 | 19970529 |
| ES 2122941 | B1 | 19990701 | | |

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     AU 9873365         A1   19981230       AU 1998-73365    19980525
     AU 730140          B2   20010301
     EP 992495          A1   20000412       EP 1998-920547   19980525
     EP 992495          B1   20040204
         R:  AT, BE, CH, DE, DK, FR, GB, IT, LI, NL, SE, PT, IE
     JP 2002502386      T2   20020122       JP 1999-500279   19980525
     AT 258920          E    20040215       AT 1998-920547   19980525
     ZA 9804466         A    19981201       ZA 1998-4466     19980526
     US 6617457         B1   20030909       US 2002-424673   20020617
PRAI ES 1997-1169       A    19970529
     WO 1998-ES145      W    19980525
AB   Quinapryl hydrochloride (I) is obtained by hydrogenolysis of quinapryl
     benzyl ester by treatment in an alc. solvent, with hydrochloric acid or
     with a solution of hydrogen chloride in isopropanol and hydrogenation;
     removing the solvent; addition of toluene to precipitate I as the toluene
solvate;
     treating said solvate with a class 3 solvent to form a solvate of
     quinapryl hydrochloride from which it can be dry-removed without degradation;
     and drying the solvate to yield I.  The crystal structures of I
     and its HCO2Et,a MeOAc solvates are also reported.
RE.CNT  3     THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD
              ALL CITATIONS AVAILABLE IN THE RE FORMAT


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     FILE 'REGISTRY' ENTERED AT 13:28:52 ON 15 APR 2004
L1             STRUCTURE UPLOADED
L2           0 S L1 EXA
L3           3 S L1 SSS FULL

     FILE 'CAPLUS' ENTERED AT 13:30:09 ON 15 APR 2004
L4          20 S L3
L5           1 S L3/PUR

=> d l3 1-3
YOU HAVE REQUESTED DATA FROM FILE 'REGISTRY' - CONTINUE? (Y)/N:y


L3   ANSWER 1 OF 3  REGISTRY  COPYRIGHT 2004 ACS on STN
RN   295792-79-9  REGISTRY
CN   3-Oxazolidineacetic acid, 4-methyl-2,5-dioxo-α-(2-phenylethyl)-,
     ethyl ester, (αS)- (9CI)  (CA INDEX NAME)
FS   STEREOSEARCH
MF   C16 H19 N O5
SR   CA
LC   STN Files:   CA, CAPLUS, CASREACT

Absolute stereochemistry.
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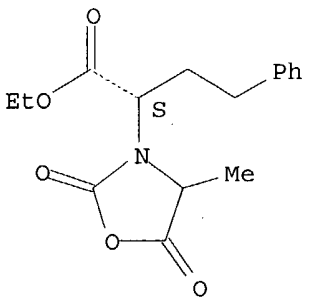


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**PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT**

               1 REFERENCES IN FILE CA (1907 TO DATE)
               1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L3   ANSWER 2 OF 3  REGISTRY  COPYRIGHT 2004 ACS on STN
RN   101820-39-7  REGISTRY
CN   3-Oxazolidineacetic acid, 4-methyl-2,5-dioxo-α-(2-phenylethyl)-,
     ethyl ester (9CI)  (CA INDEX NAME)
FS   3D CONCORD
MF   C16 H19 N O5
SR   CA
LC   STN Files:   BEILSTEIN*, CA, CAPLUS, CHEMLIST
         (*File contains numerically searchable property data)
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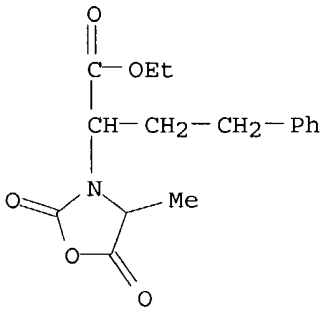
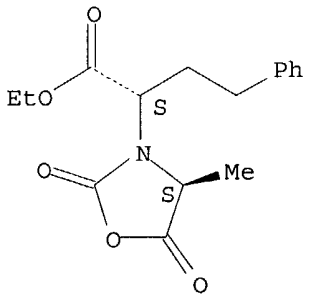


**PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT**

2 REFERENCES IN FILE CA (1907 TO DATE)
2 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L3 ANSWER 3 OF 3 REGISTRY COPYRIGHT 2004 ACS on STN
RN 84793-24-8 REGISTRY
CN 3-Oxazolidineacetic acid, 4-methyl-2,5-dioxo-α-(2-phenylethyl)-, ethyl ester, (αS,4S)- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 3-Oxazolidineacetic acid, 4-methyl-2,5-dioxo-α-(2-phenylethyl)-, ethyl ester, [S-(R*,R*)]-
OTHER NAMES:
CN N-[1(S)-Ethoxycarbonyl-3-phenylpropyl]-L-alanine N-carboxyanhydride
FS STEREOSEARCH
MF C16 H19 N O5
LC STN Files: BEILSTEIN*, CA, CAPLUS, CASREACT, CHEMCATS, CHEMLIST, USPAT2, USPATFULL
(*File contains numerically searchable property data)

Absolute stereochemistry.



**PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT**

18 REFERENCES IN FILE CA (1907 TO DATE)
18 REFERENCES IN FILE CAPLUS (1907 TO DATE)

=> d bib abs hitstr

L5 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2004 ACS on STN
AN 2001:851135 CAPLUS
DN 135:371993
TI Methods for crystallization of N-(1(S)-ethoxycarbonyl-3-phenylpropyl)-L-alanine N-carboxyanhydride
IN Fukae, Masafumi; Ueda, Yasuyoshi

PA Kaneka Corporation, Japan
SO PCT Int. Appl., 41 pp.
CODEN: PIXXD2
DT Patent
LA Japanese
FAN.CNT 1

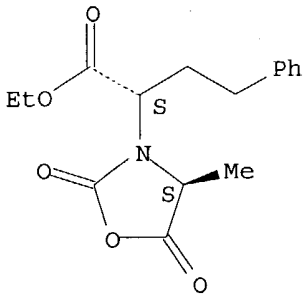
| | PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|---|
| PI | WO 2001087858 | A1 | 20011122 | WO 2001-JP4059 | 20010515 |
| | W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | | |
| | RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG | | | | |
| | AU 2001056758 | A5 | 20011126 | AU 2001-56758 | 20010515 |
| | SI 20817 | C | 20020831 | SI 2001-20002 | 20010515 |
| | EP 1283204 | A1 | 20030212 | EP 2001-930174 | 20010515 |
| | R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR | | | | |
| | TW 527351 | B | 20030411 | TW 2001-90111623 | 20010515 |
| | HR 2002000122 | A1 | 20030430 | HR 2002-122 | 20020211 |
| | US 2002137944 | A1 | 20020926 | US 2002-19318 | 20020424 |
| PRAI | JP 2000-141717 | A | 20000515 | | |
| | JP 2000-330339 | A | 20001030 | | |
| | JP 2000-352892 | A | 20001120 | | |
| | WO 2001-JP4059 | W | 20010515 | | |

AB A solution of N-(1(S)-ethoxycarbonyl-3-phenylpropyl)-L-alanine N-carboxyanhydride (I) in a good solvent therefor is added to an aliphatic hydrocarbon solvent to crystallize the N-carboxy anhydride while inhibiting the compound from separating out as an oily matter or scale. In this process, an aliphatic hydrocarbon solvent is gradually added to a solution of I in a good solvent therefor at a temperature of 60° or lower over a 1/4 h or longer to crystallize I. This process is suitable for crystallization of I in an industrial scale without oil formation or scaling to give I of high purity with large grain diameter, good powder characteristic, and good handlability. I is used as an common intermediate for a series of angiotensin converting enzyme inhibitors which are used for the treatment of hypertension. Thus, 32 g COCl2 was blown into a solution of 25 g N-[1(S)-ethoxycarbonylphenylpropyl]-L-alanine in 500 mL CH2Cl2, refluxed for 8 h on an oil bath (50°), distilled to remove CH2Cl2 containing COCl2 and HCl, and treated with CH2Cl2 to give a .apprx.62 weight% solution of I in CH2Cl2 (98% yield). The above solution (63.2 g) was added dropwise to 250 mL n-cyclohexane at -12° over a period of 1 h, stirred at the same temperature for 1 h in a good solvent/aliphatic hydrocarbon solvent weight ratio of 0.15. The precipitated I crystals were filtered under reduced pressure, washed with 50 mL n-hexane, and dried at 25° for 1 h under reduced pressure to give I (93% recovery, 98% purity, ≤99% e.e. optical purity, and average grain diameter 50 μm). An amount of scaling adhered on the wall of the vessel was .apprx.6 weight%.

IT **84793-24-8P**, N-[1(S)-Ethoxycarbonyl-3-phenylpropyl]-L-alanine N-carboxyanhydride
RL: IMF (Industrial manufacture); **PUR (Purification or recovery)**; SPN (Synthetic preparation); PREP (Preparation)
(methods for crystallization of N-[1(S)-ethoxycarbonyl-3-phenylpropyl]-L-alanine N-carboxyanhydride from combination of good solvent and aliphatic hydrocarbon)

RN 84793-24-8 CAPLUS
CN 3-Oxazolidineacetic acid, 4-methyl-2,5-dioxo-α-(2-phenylethyl)-, ethyl ester, (αS,4S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.




RE.CNT 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

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